

# Cardiac Resynchronization Therapy Improves Heart Rate Profile and Heart Rate Variability of Patients With Moderate to Severe Heart Failure

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<b>OBJECTIVES</b>	This study sought to report long-term changes of cardiac autonomic control by continuous, device-based monitoring of the standard deviation of the averages of intrinsic intervals in the 288 five-min segments of a day (SDANN) and of heart rate (HR) profile in heart failure (HF) patients treated with cardiac resynchronization therapy (CRT).
<b>BACKGROUND</b>	Data on long-term changes of time-domain parameters of heart rate variability (HRV) and of HR in highly symptomatic HF patients treated with CRT are lacking.
<b>METHODS</b>	Stored data were retrieved for 113 HF patients (New York Heart Association functional class III to IV, left ventricular ejection fraction $\leq 35\%$ , QRS $>120$ ms) receiving a CRT device capable of continuous assessment of HRV and HR profile.
<b>RESULTS</b>	The CRT induced a reduction of minimum HR (from $63 \pm 9$ beats/min to $58 \pm 7$ beats/min, $p < 0.001$ ) and mean HR (from $76 \pm 10$ beats/min to $72 \pm 8$ beats/min, $p < 0.01$ ) and an increase of SDANN (from $69 \pm 23$ ms to $93 \pm 27$ ms, $p < 0.001$ ) at three-month follow-up, which were consistent with improvement of functional capacity and structural changes. Different kinetics were observed among these parameters. The SDANN reached the plateau before minimum HR, and mean HR was the slowest parameter to change. Suboptimal left ventricular lead position was associated with no significant functional and structural improvement as well as no change or even worsening of HRV. The two-year event-free survival rate was significantly lower (62% vs. 94%, $p < 0.005$ ) in patients without any SDANN change ( $\Delta$ change $\leq 0\%$ ) compared with patients who showed an increase in SDANN ( $\Delta$ change $>0\%$ ) four weeks after CRT initiation.
<b>CONCLUSIONS</b>	Cardiac resynchronization therapy is able to significantly modify the sympathetic-parasympathetic interaction to the heart, as defined by HR profile and HRV. Lack of HRV improvement four weeks after CRT identifies patients at higher risk for major cardiovascular events. (J Am Coll Cardiol 2005;46:1875–82) © 2005 by the American College of Cardiology Foundation

Diminished heart rate variability (HRV) and increased mean heart rate (HR) in patients with heart failure (HF) are associated with a poor prognosis (1–3). There is initial evidence that cardiac resynchronization therapy (CRT) increases time-domain parameters of HRV and reduces mean HR (4–7). Similar to other interventions and drugs that improve the time-domain parameters of HRV and reduce mean HR resulting in an improved prognosis (8,9), CRT also improves short-term prognosis and reduces hospitalization rate (10,11) and mortality (12). However, data on long-term changes of time-domain parameters of HRV and HR of highly symptomatic HF patients treated with CRT devices are lacking.

Time-domain parameters of HRV in CRT patients have so far been recorded by using either conventional ambulatory Holter monitoring (4,6), by analyzing the HR histogram of sensed atrial events recorded in the CRT systems (5), or by calculating the standard deviation of a five-min median atrial-atrial sensed interval (7). Conventional HRV recording may have limited applicability for repeated measurements in daily practice. On the other hand, the standard deviation of the atrial cycle length using 10 beats/min device-based histogram resolution as calculated by Adamson et al. (5) may be not sensitive enough in recording small but meaningful changes of mean HR and time-domain parameters of HRV. Furthermore, this requires manual downloading and off-line data analysis.

The increased storage capability of the CRT devices and high reliability of their algorithms allow beat-to-beat analysis that enables continuous sampling of the minimum, maximum, and mean HR as well as repeated 24-h automatic calculation of the HRV time-domain parameters. Device-based automatic monitoring of HR and time-

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#### Abbreviations and Acronyms

CRT	= cardiac resynchronization therapy
CRT-D	= cardiac resynchronization therapy device with defibrillator back-up
HF	= heart failure
HR	= heart rate
HRV	= heart rate variability
SDANN	= standard deviation of the averages of intrinsic intervals in the 288 five-min segments of a day
SDNN	= standard deviation of RR intervals

domain parameters of HRV has been recently reported (7); this approach may be particularly helpful in evaluating long-term dynamic changes of both HR and HRV after CRT in HF patients.

We aimed to report long-term changes of cardiac autonomic control assessed by continuous, device-based monitoring of both HRV and HR profile in advanced HF patients with implanted CRT devices. Furthermore, we assessed whether different changes in HRV time-domain parameters after CRT could be associated with different prognoses.

## METHODS

**Patients.** The device-stored HR and HRV data were retrieved for 113 consecutive patients with New York Heart Association functional class III or IV, despite stable (>3 months) optimized medical therapy, left ventricular systolic dysfunction (ejection fraction  $\leq 35\%$ , end-diastolic diameter >55 mm), and ventricular conduction disturbances (QRS duration >120 ms). All patients had been hospitalized at least once in the previous year because of HF. All patients have been referred to the Division of Cardiology, University Hospital in Magdeburg for non-pharmacological treatment of HF and received a CRT device capable of continuous assessment of HRV and HR profile (Renewal I, II, and IV as well as Contak TR2, Guidant, St. Paul, Minnesota). The research protocol was approved by the locally appointed ethical committee, and all patients provided oral and written informed consent to device implantation and agreed to data retrieval and analysis.

Patients with permanent atrial fibrillation were excluded because of the inability of the device to calculate HR and HRV. Etiology was documented by coronary angiography in all patients before implantation. Mechanical asynchrony as assessed by tissue Doppler imaging was not routinely evaluated and did not constitute an inclusion criterion.

CRT was delivered by a left ventricular lead implanted into a tributary vein of the coronary sinus in addition to a standard right ventricular lead and a right atrial lead. The left ventricular lead position was reviewed by two independent investigators. The atrioventricular delay was optimized by invasive monitoring of pulse pressure or left ventricular

dP/dt as reported by Auricchio et al. (13). All CRT devices were programmed in atrial-synchronous biventricular pacing with the lower rate limit set at 40 beats/min, and the upper rate limit was set at 130 beats/min.

After implantation, the first follow-up was performed at one month, then at the third and sixth month and then every six months. At each follow-up, stored data including arrhythmic episodes were retrieved and saved onto disks for further off-line analysis. Echocardiographic evaluation and symptom-limited cardiopulmonary exercise testing were performed before, 6 months after, and 12 months after CRT implantation.

Major cardiac events were considered as death for any cause, implantation of a left ventricular assist device or urgent heart transplantation, hospitalization for cardiovascular reasons, and DC shock by device for ventricular arrhythmias.

**HR profile and HRV evaluation.** The Contak Renewal devices enable automatic continuous recording of the following parameters: minimum HR, mean HR, maximum HR, and standard deviation of the averages of intrinsic intervals in the 288 five-min segments of a day (SDANN). For each parameter the weekly averages are provided. Paced atrial beats, supraventricular and ventricular premature beats, and arrhythmic episodes are excluded from the analysis by the device. Furthermore, the devices provide the percentage of time during the 24-h collection period in which there were valid intrinsic atrial beats. If this percentage falls below 67%, data will not be displayed for that collection period. Baseline value of mean HR, minimum HR, maximum HR, and SDANN are considered the average of the first week after CRT implantation.

**Statistics.** All data are expressed as mean  $\pm$  standard deviation. An exponential fitting equation (Appendix) was used to describe the dynamic changes of HR and SDANN. The values at 90%, 95%, and 99% of the plateau are reported. Comparisons between baseline and plateau values of each considered parameter were made using a paired Student *t* test. Comparisons between groups were performed using an unpaired Student *t* test and a chi-square test. The difference in cardiac event rate over time was analyzed by Kaplan-Meier and log-rank tests; SPSS software version 10 (SPSS Inc., Chicago, Illinois) was used, and for all tests the level of significance was set at a value of 0.05.

## RESULTS

Table 1 summarizes the clinical and demographic characteristics of the whole population. Most of the patients were men presenting with coronary artery disease, depressed left ventricular ejection fraction, and severely dilated ventricles, in advanced functional class despite best optimized medical therapy. About 37% of patients suffered from diabetes. The vast majority of patients (82%) received a CRT device with a cardioverter-

**Table 1.** Clinical Characteristics of the Study Population

Number of patients	113
Male (%)	78
Age (yrs)	62 ± 9
CAD (%)	60
Diabetes (%)	37
NYHA functional class III/IV	106/7
Ejection fraction (%)	21 ± 6
LVEDD (mm)	69 ± 9
Peak VO <sub>2</sub> (ml/kg/min)	14.3 ± 3.5
QRS duration (ms)	159 ± 27
Mean PCWP (mm Hg)	15 ± 10
ACE-I/ARB (%)	98
Beta-blockers (%)	96
Aldosterone antagonists (%)	34
Diuretics (%)	100
Digitalis (%)	50
Amiodarone (%)	16
CRT-D (%)	82

ACE-I = angiotensin-converting enzyme inhibitors; ARB = AT1 receptor blockers; CAD = coronary artery disease; CRT-D = cardiac resynchronization therapy device with defibrillator back-up; LVEDD = left ventricular end-diastolic diameter; NYHA = New York Heart Association; peak VO<sub>2</sub> = oxygen consumption at peak exercise; PCWP = pulmonary capillary wedge pressure.

defibrillator back-up (CRT-D), which was indicated because of a history of ventricular arrhythmias (29%) or for primary prevention of sudden cardiac death (71%). About 16% of patients received amiodarone for atrial fibrillation prevention or suppression of runs of ventricular tachycardia. The vast majority of patients (82%) underwent de novo implantation, and 20 patients received a device replacement 43 ± 18 months after the first CRT implantation.

Clinical follow-up and device interrogation were possible in all patients. Frequent paroxysmal episodes of atrial fibrillation were recorded in 13 patients, and marked sinus bradycardia requiring continuous atrial-based pacing occurred in 6 patients. Both conditions prevented automatic calculation of time-domain parameter of HRV and recording of HR profile. The demographic, echocardiographic, and hemodynamic parameters of these patients did not differ in any way from those of the 94 patients (83%) who maintained stable sinus rhythm for at least one year after implantation.

Except for diuretics, which were frequently reduced, no further dosage adjustment of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers was usually

made. No patient was crossed over to any other beta-blocking agent, but dosage increase was attempted in six patients four to six months after implantation.

**HR profile and HRV after CRT implantation.** A significant reduction of minimum HR (from 63 ± 9 beats/min to 58 ± 7 beats/min,  $p < 0.001$ ) and mean HR (from 76 ± 10 beats/min to 72 ± 8 beats/min,  $p < 0.01$ ) occurred. This was concurrent with a significant increase of SDANN (from 69 ± 23 ms to 93 ± 27 ms,  $p < 0.001$ ) and maximum HR (from 95 ± 10 beats/min to 98 ± 11 beats/min,  $p < 0.01$ ) three months after starting CRT in patients with de novo implantation (Table 2). The magnitude of the changes from baseline to three months was similar in both patients with coronary artery disease and idiopathic dilated cardiomyopathy as well as in both diabetic and non-diabetic patients.

Characteristic dynamic changes of SDANN, mean HR, minimum HR, and maximum HR were observed. Apart from maximum HR, in all cases of new device implantation there was a monotonic exponential distribution of the data points (Appendix). The exponential curves that best fit the overall data as well as the mean based on raw data at one week and at 90%, 95%, and 99% of the plateau in patients with new device implantation are presented in Figure 1. In these patients, most of the changes occurred within 12 weeks after device implantation. However, different kinetics were observed among parameters. The SDANN reached the 90%, 95%, and 99% of the plateau value before minimum HR. Mean HR was the latest parameter to change (Fig. 1).

**New implantation versus device replacement.** Patients with de novo implantation differed from the others (Table 3) because they had a more prevalent ischemic etiology ( $p < 0.01$ ) and more frequently received a CRT-D device ( $p < 0.01$ ). All other clinical, echocardiographic, and hemodynamic parameters were not significantly different between the two groups.

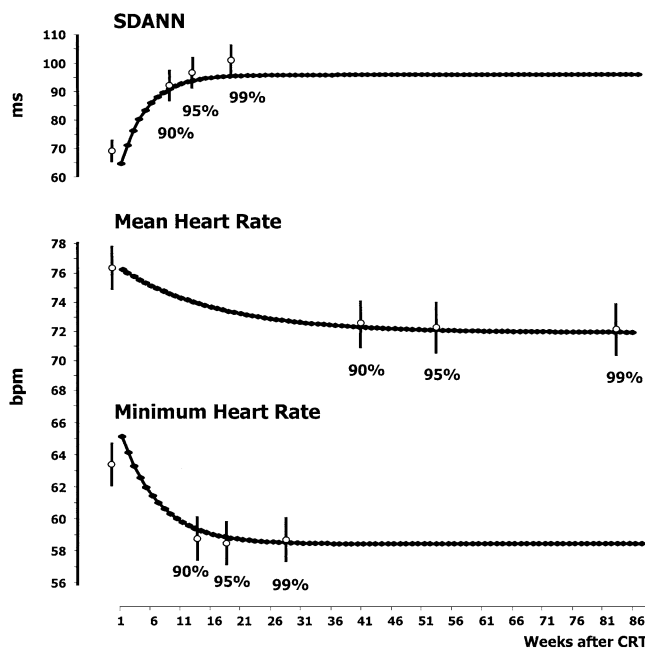
In patients in whom a CRT device was replaced with a new one capable of automatic monitoring of HRV, SDANN showed higher first-week and second-week values compared with patients with de novo implantation (Table 2). Subsequently, patients with a device replacement showed a small but insignificant change of mean HR and SDANN three months after replacement. The values of mean HR

**Table 2.** Changes of HR Profile and of SDANN in Patients With De Novo Implantation of a CRT Device and in Those With a Device Replacement

	De Novo CRT			Replacement CRT		
	Baseline	2 Weeks	3 Months	Baseline	2 Weeks	3 Months
Minimum HR (beats/min)	63 ± 9	61 ± 10*	58 ± 7*	61 ± 8	60 ± 6	61 ± 3
Mean HR (beats/min)	76 ± 10	74 ± 11	72 ± 8*	75 ± 10	76 ± 7	74 ± 6
Maximum HR (beats/min)	95 ± 10	97 ± 13*	98 ± 11	94 ± 14	98 ± 13	103 ± 7
SDANN (ms)	69 ± 23	84 ± 29*	93 ± 27*	87 ± 27	91 ± 12	100 ± 22

\*Significantly different ( $p < 0.005$ ) compared with previous follow-up. Baseline values refers to averages of the first week after implantation.

CRT = cardiac resynchronization therapy; HR = heart rate; SDANN = standard deviation of the averages of intrinsic intervals in the 288 five-minute segments of a day.



**Figure 1.** Dynamic changes of standard deviation of the averages of intrinsic intervals in the 288 five-min segments of a day (SDANN), mean heart rate (HR), and minimum HR based on fitted data (filled circles). For baseline, 90%, 95%, and 99% of the value to plateau, the mean value based on the raw data (open circles) is reported with the standard error (Y axis).

and SDANN reached two weeks after replacement were not significantly different from those recorded three months after implantation in patients who received a new device (Table 2).

**HRV changes after CRT and outcome.** Among patients who maintained stable sinus rhythm and received a de novo CRT device (74 patients), nine patients (12%) experienced a major cardiac event over two years of follow-up. Two

**Table 3.** Clinical Characteristics of Patients With De Novo Implantation of a CRT Device and of Those With a Device Replacement

	De Novo CRT	Replacement CRT	p Value
Number of patients	93	20	
Male (%)	80	70	NS
Age (yrs)	63 ± 9	61 ± 7	NS
CAD (%)	67	30	<0.01
Diabetes (%)	36	47	NS
NYHA functional class III/IV	86/7	20/0	NS
Ejection fraction (%)	20 ± 6	22 ± 5	NS
LVEDD (mm)	68 ± 8	70 ± 10	NS
Peak $\text{VO}_2$ (ml/kg/min)	13.4 ± 2.9	15.3 ± 2.3	NS
QRS duration (ms)	155 ± 25	166 ± 28	NS
Mean PCWP (mm Hg)	15 ± 10	14 ± 10	NS
ACE-I/ARB (%)	98	100	NS
Beta-blockers (%)	96	95	NS
Aldosterone antagonist (%)	37	20	NS
Diuretics (%)	100	100	NS
Digitalis (%)	46	65	NS
Amiodarone (%)	17	10	NS
CRT-D (%)	88	60	<0.01

Abbreviations as in Table 1.

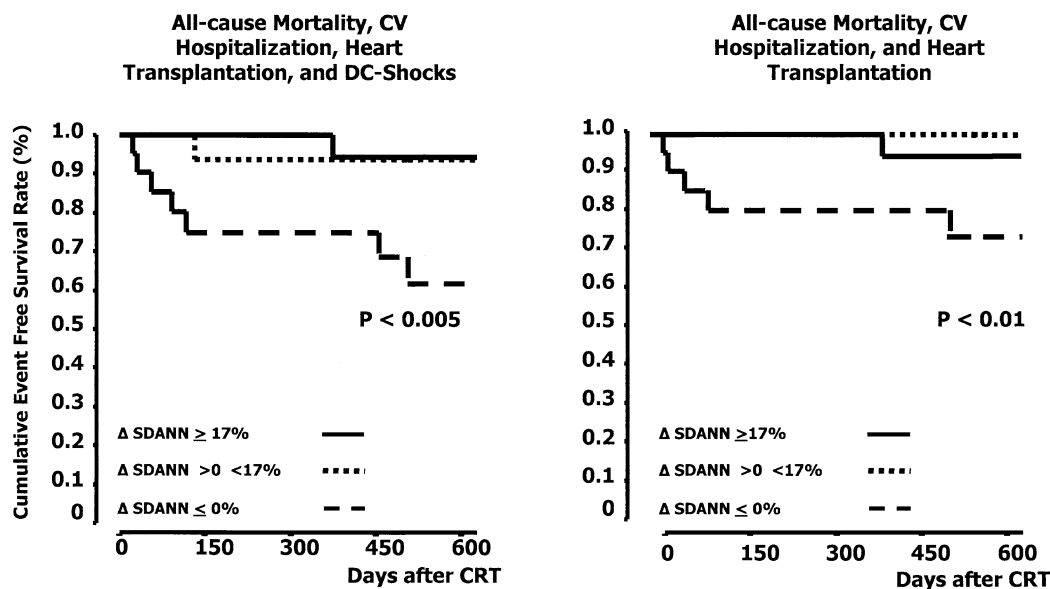
patients died (one because of HF and one due to myocardial infarction), one underwent urgent cardiac transplantation, three were hospitalized because of HF, and three received an appropriate shock from the implantable cardioverter defibrillator device. The two-year event-free survival rate was significantly different ( $p < 0.005$ ) based on the change of SDANN four weeks after implantation (Fig. 2). Patients in whom SDANN failed to increase or even worsened (first tertile of SDANN delta change,  $\leq 0\%$ ) had the lowest two-year event-free survival rate (62%). Indeed, nearly all cardiac events (seven of nine) occurred in these patients; the mean time to first event was  $87 \pm 34$  days. By contrast, patients in whom minor (second tertile, SDANN delta change ranging from 0% to 17%) or large (third tertile, SDANN delta change  $\geq 17\%$ ) changes of SDANN were recorded had two-year event-free survival rates as high as 94% (Fig. 2). The difference also remained statistically significant among strata ( $p < 0.01$ ) when DC shocks were excluded (Fig. 2).

Based on changes of HRV after CRT, non-responders to CRT were defined as patients ( $n = 26$ ) in whom SDANN failed to improve or even worsened (SDANN delta change  $\leq 0\%$ ) four weeks after implantation. Responders to CRT were considered to be those patients ( $n = 48$ ) who showed an increase of SDANN (SDANN delta change  $> 0\%$ ) four weeks after starting CRT.

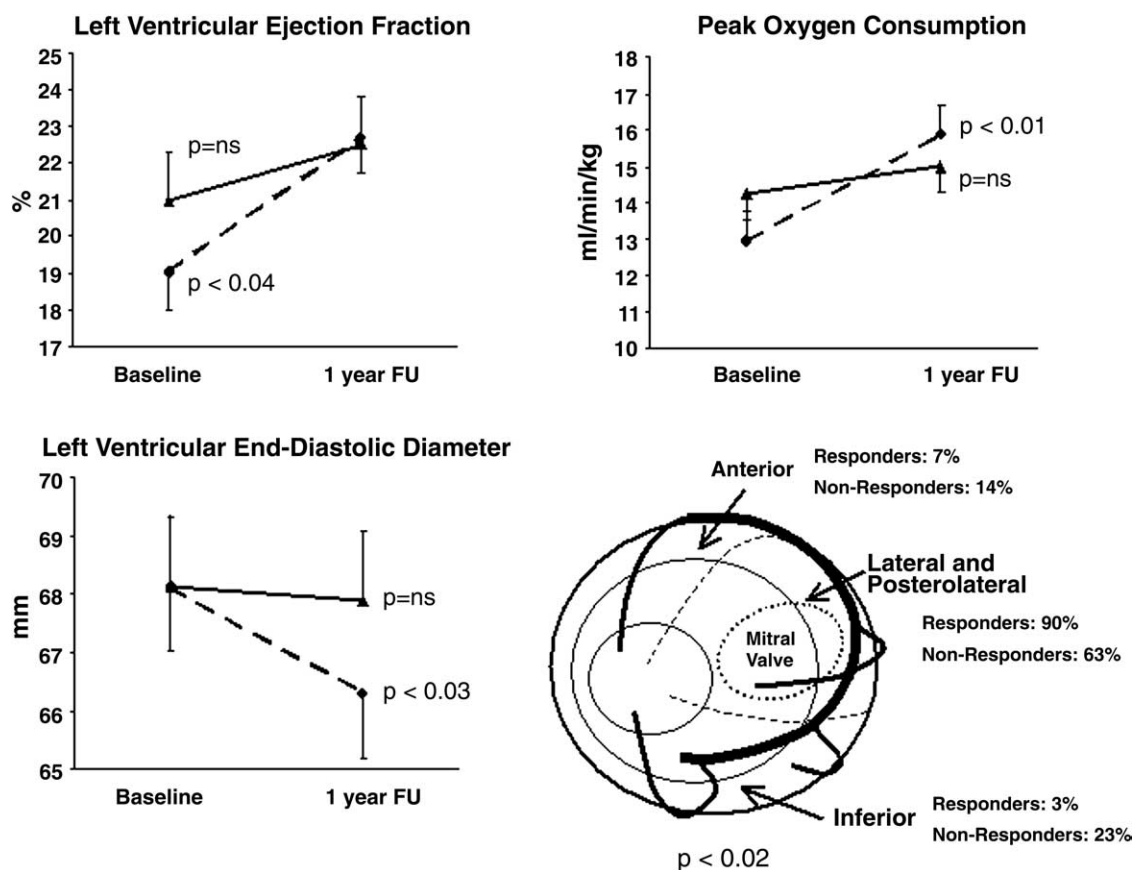
At baseline, responders and non-responders to CRT did not significantly differ in any clinical, echocardiographic, or hemodynamic parameter. Nevertheless, the left ventricular lead tip position significantly differed (Fig. 3), being more frequently placed in a lateral or posterolateral region in responders compared with non-responders (90% vs. 63%,  $p < 0.02$ ). At one-year follow-up, only responders showed a statistically significant improvement of peak  $\text{VO}_2$  consumption, left ventricular ejection fraction, and left ventricular end-diastolic diameter (Fig. 3).

## DISCUSSION

The results of this study show that in symptomatic HF patients, CRT determines long-term sustained changes of HRV and HR profile that are consistent with improvement of functional capacity and structural changes. The changes of these parameters usually peaked within a few months after implantation of a new CRT device, and remained stable years thereafter. The dynamic changes of SDANN, mean HR, and minimum HR were similar, but they peaked at different times after starting CRT, with SDANN being the earliest parameter to change. Lack of increase in SDANN four weeks after CRT implantation identified patients at highest risk for major cardiovascular events such as death, urgent heart transplantation, DC shock for fast ventricular tachyarrhythmias, and hospitalization for cardiovascular reasons. Moreover, these patients showed no significant improvement of exercise capacity and no significant change in left ventricular ejection fraction and end-diastolic



**Figure 2.** The two-year cumulative event-free survival rate in patients with no changes in standard deviation of the averages of intrinsic intervals in the 288 five-minute segments of a day (SDANN) four weeks after implantation (first tertile,  $\Delta$  change  $\leq 0\%$ ), in patients with some SDANN changes (second tertile,  $\Delta$  change from 0 to 17%), and in those with large SDANN changes (third tertile,  $\Delta$  change  $\geq 17\%$ ). CRT = cardiac resynchronization therapy; CV hospitalization = hospitalizations for cardiovascular reasons.



**Figure 3.** Change of left ventricular ejection fraction, left ventricular end-diastolic diameter, and oxygen consumption at peak exercise from baseline to one-year follow-up (FU) in responders (dotted lines) and non-responders (continuous lines) to cardiac resynchronization therapy (CRT), according to changes of standard deviation of the averages of intrinsic intervals in the 288 five-minute segments of a day (SDANN) four weeks after CRT implantation. The vertical bars represent the standard error. The p values refer to comparison between baseline and follow-up among each group. (Bottom right) distribution of locations of the left ventricular lead tip in a left anterior oblique (LAO) 40° view among responders and non-responders. The p value refers to comparison between responders and non-responders.



diameter, which was most likely due to suboptimal left ventricular lead implantation.

**Automatic monitoring of HR profile and HRV.** Device-based continuous monitoring of autonomic tone balance is an appealing technological advance with large therapeutic and possibly prognostic implications. Adamson et al. (7) have recently reported that full automatic device-based monitoring of time domain parameters of HRV is feasible. Our data recorded over a longer follow-up time confirm the observations of Adamson et al. (7). Although the device automatically evaluates parameters such as mean HR, HR range, and SDANN, at the present time manual downloading at each follow-up visit is still required. Device evolution and improved internet-based database capability may enable automatic downloading, thus providing daily access to patient's stored data.

Automatic monitoring of either HR profile or HRV time-domain parameters may help in forecasting major cardiovascular events in CRT patients. Our data indicate that each monitored parameter stabilizes at several weeks after initiation of CRT, with SDANN being the first parameter to both change and reach a plateau. Thus, timely recognition of drift from its initial value may be used for warning (7).

**Effect of CRT on HR profile and HRV.** This study shows that HF patients with ventricular conduction disturbances who remain symptomatic despite tailored medical therapy, have low SDANN values, and have high mean HR at baseline. In these patients, CRT showed a favorable effect on sympathovagal balance with a withdrawal of sympathetic dominance as shown by the increase of SDANN and the reduction of mean HR. The changes in HR and HRV recorded in our patients were similar to those observed by Alonso et al. (4), Adamson et al. (5,7), and Livanis et al. (6) at similar follow-up periods. These changes were parallel to improvements of functional capacity and ventricular function.

Our findings expand previous knowledge showing a time-dependent effect of CRT on SDANN and HR profile with the data showing an exponential curve. The increase of HRV and the reduction of mean HR were mostly observed after three to four months of CRT and then remained stable for years. Indeed, the second week values of SDANN, mean HR, and minimum HR of patients in whom a CRT device was replaced (usually three to four years after first implantation) were very similar to those of de novo patients recorded at three months of follow-up.

Values of SDANN below 120 ms are abnormal, and those in the range of 50 to 70 ms in a patient cohort similar to our study population have been reported to be associated with poor prognosis (2). By contrast, patients with SDANN values above this cut-off have a better outcome (2). In the majority of our patients we observed an increase of SDANN ranging in values from 60 to 70 ms at baseline to 90 to 100 ms or more after CRT. This may suggest a reduced probability of cardiovascular events. Indeed, in those pa-

tients in whom SDANN increased, rare cardiovascular events or implantable cardioverter defibrillator shocks occurred over the follow-up period. In contrast, in about 30% of our patients, SDANN either did not change or reduced even further after CRT, which resulted in a 38% two-year cumulative event rate incidence. Adamson et al. (7) used the average HRV value measured between five to eight weeks after implantation for risk stratification showing that a low SDANN value was associated with increased mortality risk. In contrast, we considered the prognostic value of HRV changes induced by CRT. Furthermore, compared with the analysis of Adamson et al. (7), who excluded the first four weeks after CRT implantation, this study has shown that this period of time is particularly useful for recognizing patients at high risk of further events. This observation needs to be further evaluated in a larger prospective controlled study.

Our patient cohort was similar to the patients included in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial (11). In this study the survival curves of CRT and CRT-D patients showed a different behavior; the two survival curves separated early on and thereafter remained parallel (11). Intriguingly, readjustment of the sympathovagal balance with a withdrawal of sympathetic dominance was particularly pronounced during the first three months in our patients and was completed about six months after device implantation (99% of the SDANN plateau). This may suggest a lower likelihood of developing ventricular tachyarrhythmias after a certain period of CRT, as reported by Higgins et al. (14).

**Underlying pathophysiological mechanisms.** The CRT-induced hemodynamic changes are usually considered to be the unique mechanism responsible for the positive effect of the therapy. Indeed, most studies have so far emphasized the importance of improved coordination of the septal and lateral wall contraction (13), reduction of mitral regurgitation, and improvement of ventricular filling (15,16). Our data possibly suggest a further mechanism that may improve cardiac efficiency, i.e., slowing of the HR. This may have a beneficial effect on diastolic times and on myocardial oxygen demand. Interestingly, the absolute and relative magnitude of the change of HR during CRT is similar to that observed during beta-blocker treatment for patient populations presenting similar clinical characteristics (17,18).

We observed that SDANN changes preceded HR changes after CRT. There are at least two possible explanations for the improvement in HRV after CRT. Sensory input from cardiac receptors to the central nervous system is profoundly altered in patients with cardiac disease by a variety of mechanisms including ischemia, as well as mechanical distortion of afferent fibers in the presence of abnormalities in regional contraction and in the geometry of the beating heart (19). Deranged inputs from cardiac receptors might be restored by CRT with an ensuing reduction in sympatho-excitation. This would restore tonic vagal efferent activity to the sinus node. The effects of

unloading ventricular cardio-inhibitory receptors (20) or improved ventricular filling capacity might also play a role. In particular, partial or complete removal of such a reflex may become evident once reverse ventricular remodeling has fully taken place, usually at around three to six months after starting CRT (21). Furthermore, altered ventricular contraction patterns depending on both the underlying cardiomyopathy and the conduction defects lead to an altered arterial pressure profile that affects autonomic modulation via the arterial baroreceptors. Changes in dP/dt may positively affect baroreflex modulation of autonomic activity resulting in a decrease in sympathetic and an increase in vagal efferent activity at the sinus node. Direct recordings of sympathetic neural activity in patients with reduced left ventricular systolic function were obtained by Hamdan et al. (22), who showed a significant reduction of neural activity after left ventricular and biventricular pacing.

These pathophysiological hypotheses are strengthened by the evidence that in those patients in whom unchanged modulation or worsening of autonomic nervous system balance occurred during CRT, left ventricular lead position was suboptimal. This has possibly resulted in a suboptimal delivery of CRT leading to no improvement in oxygen consumption at peak exercise, no major structural changes, and poor outcome.

All together, the data of this study suggest that CRT can act through several cardiac and systemic mechanisms to modulate the autonomic nerve system. These data are consistent with recent findings showing reduction of the systemic level of norepinephrine and brain natriuretic peptide after CRT (23,24). However, further prospective studies with serial assessment of autonomic tone including neurohumoral evaluation are warranted.

**Study limitations.** Possible limitations of our study are the relatively small sample size and the lack of autonomic tone assessment before and after the implantation of a CRT device. We assessed SDANN changes instead of standard deviation of RR intervals (SDNN), the latter being more frequently used for evaluating autonomic nerve system activity. However, SDANN and SDNN are closely related, have a high reproducibility, and have similar stability over time (25,26). The dynamic changes observed after implantation may be related to implant procedure and consequent reduced physical activity during hospitalization. At the present time, the impact of bed rest, anesthesia, implantation procedure, and other factors on HR profile and HRV is unknown. However, comparison of dynamic changes for each parameter between patients with a de novo implantation and those receiving a device replacement clearly showed that two weeks after implantation patients with device replacement reached a plateau that overlapped the values reached three months after implantation by the patients with de novo implantation. Finally, the small number of cardiovascular events occurring in patients with CRT did not allow us to further analyze the impact of HF exacerbation and optimization of the device on the autonomic

profile. However, this issue has been investigated in great detail in a larger number of patients and events by Adamson et al. (7).

## CONCLUSIONS

This study showed that CRT significantly modified the sympathetic-parasympathetic influence to the heart, as assessed by HR profile and HRV. Significant changes of HRV time-domain parameters and HR profile were observed shortly after CRT and were sustained for years thereafter. This positive effect on autonomic nervous system modulation was consistent with improvement of functional capacity and reverse remodeling. Suboptimal left ventricular lead position was associated with no significant functional and structural improvement as well as no change or even worsening of HRV. Lack of HRV improvement four weeks after CRT identified patients at higher risk for major cardiovascular events, including death, urgent heart transplantation, hospitalization for cardiovascular reasons, and ventricular arrhythmias. Thus, SDANN may be a useful, objective, and early parameter for identifying patients who may or may not respond to CRT and who may require additional interventions.

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## APPENDIX

For the exponential fitting equation, please see the online version of this article.